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Antiviral Efficacy of Favipiravir against Two Prominent Etiological Agents of Hantavirus Pulmonary Syndrome

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Hantavirus pulmonary syndrome (HPS) is caused by infection with several *Sigmodontinae*- and *Neotominae*-borne hantaviruses and has a case fatality rate of 30 to 50%. Humans often become infected by inhalation of materials contaminated with virus-laden rodent urine or saliva, although human-to-human transmission has also been documented for Andes virus (ANDV). The ability to transmit via aerosolization, coupled with the high mortality rates and lack of therapeutic options, makes the development of medical countermeasures against HPS imperative. In the present study, we evaluated the efficacy of the broad-spectrum antiviral agent favipiravir (T-705) against Sin Nombre virus (SNV) and ANDV, the predominant causes of HPS in North and South America, respectively. *In vitro*, T-705 potently inhibited SNV and ANDV, as evidenced by decreased detection of viral RNA and reduced infectious titers. For both viruses, the 90% effective concentration was estimated at ≤5 μg/ml (≤31.8 μM). In the lethal ANDV hamster model, daily administration of oral T-705 at 50 or 100 mg/kg of body weight diminished the detection of viral RNA and antigen in tissue specimens and significantly improved survival rates. Oral T-705 therapy remained protective against HPS when treatment was initiated prior to the onset of viremia. No disease model for SNV exists; however, using a hamster-adapted SNV, we found that daily administration of oral T-705 significantly reduced the detection of SNV RNA and antigen in tissue specimens, suggesting that the compound would also be effective against HPS in North America. Combined, these results suggest that T-705 treatment is beneficial for postexposure prophylaxis against HPS-causing viruses and should be considered for probable exposures.

In humans, hantaviruses (family *Bunyaviridae*, genus *Hantavirus*) are responsible for two diseases, hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) (1). Hantaviruses that are pathogenic to humans are maintained in nature and transmitted to humans through specific rodent hosts that dictate the geographic ranges of the two diseases (2). HFRS occurs primarily in Europe and Asia and is associated with infection with Old World hantaviruses, including Hantaan and Dobrava viruses, while HPS has been documented throughout the Americas and is caused by infection with New World hantaviruses, including Sin Nombre and Andes viruses (SNV and ANDV, respectively) (2, 3). Typically, HPS occurs sporadically, with relatively few cases noted in the same temporal span and geographical region, although outbreaks have been documented, including the recent cluster of cases originating in Yosemite National Park in California (4–6). Both HFRS and HPS are associated with systemic infection of endothelial cells leading to vascular leakage; however, the two diseases have distinct clinical presentations, with HFRS primarily affecting the kidneys and HPS targeting the lungs. The target organ of each disease may in part explain the vast differences in mortality rates. While HFRS is fatal in as many as 15% of diagnosed cases, case fatality rates for HPS can reach 50% (2).

Despite their global distribution and the significant morbidity and mortality attributed to this group of viruses, there are currently no U.S. Food and Drug Administration (FDA)-approved therapeutics or vaccines to treat or prevent HFRS or HPS. The broad-spectrum antiviral agent ribavirin has been shown to reduce the severity of HFRS in clinical trials in China and Korea, although its efficacy is dependent on early initiation of treatment (7, 8). Recently, ribavirin was shown to prevent lethal HPS disease in the hamster model, with efficacy dependent on the time of initiation of therapy (9). These findings support previous clinical trials conducted in North America which found that ribavirin therapy was ineffective against HPS when treatment was initiated after respiratory symptoms were apparent (10, 11). Aside from ribavirin, few antiviral compounds have been tested in animal models against HPS or HFRS, and none have been reported to show efficacy against infection or the ensuing disease (12).

T-705 (favipiravir; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is a pyrazine derivative that, like ribavirin, has broad-spectrum antiviral activity against several RNA viruses, including seasonal influenza virus as well as highly pathogenic H5N1 and drug-resistant H1N1 strains (13–15), West Nile virus (16), norovirus (17), and the arenaviruses Junin virus, Guanarito virus, Pichinde virus, and Tacaribe virus (18–20). T-705 has also been shown to be highly active against bunyaviruses, including La Crosse, Punta Toro, Rift Valley fever, and sandfly fever viruses (18). For most of these viruses, *in vitro* studies demonstrated that the antiviral activity of T-705 was similar to, if not better than, that of ribavirin (21). Importantly, unlike ribavirin, which is associated with hemolytic anemia, T-705 is well tolerated in humans, with no

Received 26 April 2013 Returned for modification 31 May 2013
Accepted 5 July 2013
Published ahead of print 15 July 2013
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doi:10.1128/AAC.00886-13

side effects noted in human clinical trials. Supporting the low toxicity of this compound, the 50% lethal dose (LD_{50}) of T-705 is at least 6 times greater than that of ribavirin in hamsters (18, 21).

Recently, T-705 was shown to be effective at reducing the replication of Maporal virus, a South American hantavirus (22). The purpose of the studies outlined here was to expand on these findings and evaluate the efficacy of T-705 against the most prominent etiological agents of HPS in North and South America, SNV and ANDV, respectively, using both *in vitro* and *in vivo* models.

MATERIALS AND METHODS

Ethics statement. All animal experiments were approved by the Institutional Animal Care and Use Committee of the Rocky Mountain Laboratories (approval ID 2012-34) and were performed according to the guidelines of the Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC) by certified staff in an AAALAC-approved facility.

Biosafety. ANDV (strain Chile 9717869) and SNV (strain 77734) were propagated, and their titers were determined, on Vero cells by using previously described methods (23) in a biosafety level 3 (BSL3) facility. All work with infected hamsters and potentially infectious materials derived from hamsters was conducted in a BSL4 facility at Rocky Mountain Laboratories. Samples were inactivated and removed according to standard operating protocols approved by the local Institutional Biosafety Committee.

Test compounds. T-705 was provided by the Toyama Chemical Company, Ltd. (Tokyo, Japan). Ribavirin was provided by ICN Pharmaceuticals (Costa Mesa, CA). For *in vivo* studies, the antiviral compounds were resuspended in sterile water containing 0.4% carboxymethyl cellulose.

***In vitro* efficacy studies.** In order to determine the 90% effective concentration (EC_{90}) of T-705 against ANDV and SNV, nearly confluent (>95%) monolayers of Vero cells were infected at a multiplicity of infection (MOI) of 0.01. After 1 h of absorption, cells were washed and the inoculum replaced with a culture medium (Dulbecco's modified Eagle's medium [DMEM] supplemented with 2% fetal bovine serum, 100 U ml^{-1} penicillin, 100 μg ml^{-1} streptomycin, and 2 mM L-glutamine) containing varying concentrations (0, 0.05, 0.1, 0.25, 0.5, 1, 2.5, 5, 12.5, 25, or 50 μg ml^{-1}) of T-705. On days 3, 5, and 7 postinfection, representative samples of infected cells and supernatants were collected for quantitative reverse transcription-PCR (qRT-PCR) analysis as well as for the determination of infectious titers as described previously (9). Cell viability was assessed visually at the time of sample collection.

Animals. Female Syrian hamsters (*Mesocricetus auratus*) (Harlan Laboratories, Indianapolis, IN) 4 to 6 weeks of age and weighing 80 to 95 g were sorted prior to the start of experiments to ensure that the average weights were similar across all groups. For ANDV experiments, hamsters were inoculated by intraperitoneal (i.p.) injection with 100 LD_{50}s, representing an approximate challenge dose of 154 focus-forming units (FFU), diluted in sterile DMEM. For SNV experiments, hamsters were inoculated by i.p. injection with 400 μl of a 10% (wt/vol) lung homogenate containing SNV that had been passaged 20 times in Syrian hamsters and had been shown to result in systemic and prolonged infections in hamsters (24).

***In vivo* efficacy studies.** Two independent experiments were conducted to determine the efficacy of T-705 treatments in preventing lethal HPS in ANDV-infected hamsters. The first experiment consisted of a dose-response study in which six groups of 9 hamsters were inoculated with ANDV and were dosed by oral gavage using an 18-gauge ball-tipped feeding needle with 100, 50, 20, 5, 1, or 0 (placebo) mg of T-705/kg of body weight/day. Twice-daily treatments were initiated 1 day postinfection and continued for 14 consecutive days. Two groups of 3 hamsters were mock infected with sterile DMEM alone and were treated on the same schedule with 100 mg T-705/kg/day or vehicle only. A group of 9 ANDV infected hamsters was included as a positive treatment control group and was similarly treated with 20 mg of ribavirin/kg/day, a dose known to prevent lethal HPS in hamsters (9). On day 8 postinfection, 3 hamsters per treatment group were anesthetized, weighed, and exsanguinated by cardiac puncture. The lungs were removed and weighed in order to calculate the ratio of lung weight to body weight. Lungs were bisected with small hemostats, and one section was insufflated with, and then submerged in, 10% formalin, while the other half was inactivated in lysis buffer RLT. Blood samples were inactivated in lysis buffer AVL. The remaining 6 animals per group were monitored for disease progression and survival for 35 days.

In a second study, the efficacy of delayed T-705 treatment was assessed. Five groups of 6 hamsters were infected with ANDV as outlined above. On each of days 3, 4, 5, and 6 postinfection, twice-daily oral T-705 treatments were initiated for a single group of hamsters. The fifth group was treated with the vehicle beginning on day 3 postinfection. To account for the high level of ANDV replication at the time of initiation of therapy, a loading dose of 300 mg/kg was administered on the first day of treatment. Subsequent doses were 200 mg/kg/day, and treatment lasted for 14 consecutive days. To determine whether animals were viremic at the time of treatment initiation, a small blood sample (200 μl) was collected from the retro-orbital sinus of each hamster. For both experiments, seroconversion was assessed in convalescent-phase serum samples collected from surviving hamsters by using a recombinant SNV nucleocapsid protein-based enzyme-linked immunosorbent assay (ELISA), as described previously (25).

Currently no disease model for SNV exists; however, an infection model based on a serially passaged hamster-adapted SNV (HA-SNV) was described recently (24). Therefore, to evaluate the effect of T-705 on SNV replication *in vivo*, three groups of 6 hamsters were infected with HA-SNV (10% [wt/vol]) via i.p. injection. Beginning at 1 day postinfection, a single group of hamsters was treated orally with either 100 mg of T-705/kg/day, 20 mg of ribavirin/kg/day, or the vehicle only. To assess the efficacy of treatments, hamsters were euthanized on day 8 postinfection (a time when ANDV-infected hamsters began to demonstrate signs of illness), and samples (blood and lung) were collected as outlined above to determine the extent of viral replication.

ANDV- and SNV-specific qRT-PCR. Total RNA was extracted from cells and solid tissue (approximately 30-mg pieces) using RNeasy minikits and from cell culture supernatants and blood using QIAamp viral RNA kits (both from Qiagen, Valencia, CA). Viral RNA was quantified on a Rotor-Gene 6000 instrument (Corbett Life Science, Sydney, Australia) with QuantiFast probe reagents (Qiagen) by using previously described real-time RT-PCR assays specific for the ANDV or SNV nucleocapsid protein-coding region (23, 26).

Histology and IHC. Formalin-fixed lung samples were embedded in paraffin, processed according to standard procedures, and either stained with hematoxylin and eosin or tested by immunohistochemistry (IHC) for the presence of viral antigen by using polyclonal rabbit antisera generated against a recombinant SNV nucleocapsid protein as described previously (9, 27). Slides were evaluated by a veterinary pathologist.

Statistical analysis. Statistical differences between treatment groups were examined using one-way analysis of variance with the Tukey-Kramer multiple-comparison posttest. Survival rates were compared using Fisher's exact test.

RESULTS

***In vitro* effect of T-705 on SNV and ANDV replication.** Treatment of ANDV- and SNV-infected Vero cells with T-705 diminished viral RNA synthesis and infectious virus titers in a dose-dependent manner (Fig. 1). The levels of viral RNA detected in extracts from cell pellets and supernatants were reduced by more than 100- and 1,000-fold for SNV- and ANDV-infected cell cultures, respectively, at T-705 concentrations of 25 μg/ml or greater (Fig. 1A to D). Measurement of the infectious titers of ANDV and SNV grown in the presence of varying concentrations of T-705 showed that the EC_{90} was between 2.5 and 5 μg/ml (15.9 to 31.8 μM) (Fig. 1E). Concentrations of T-705 greater than 5 μg/ml

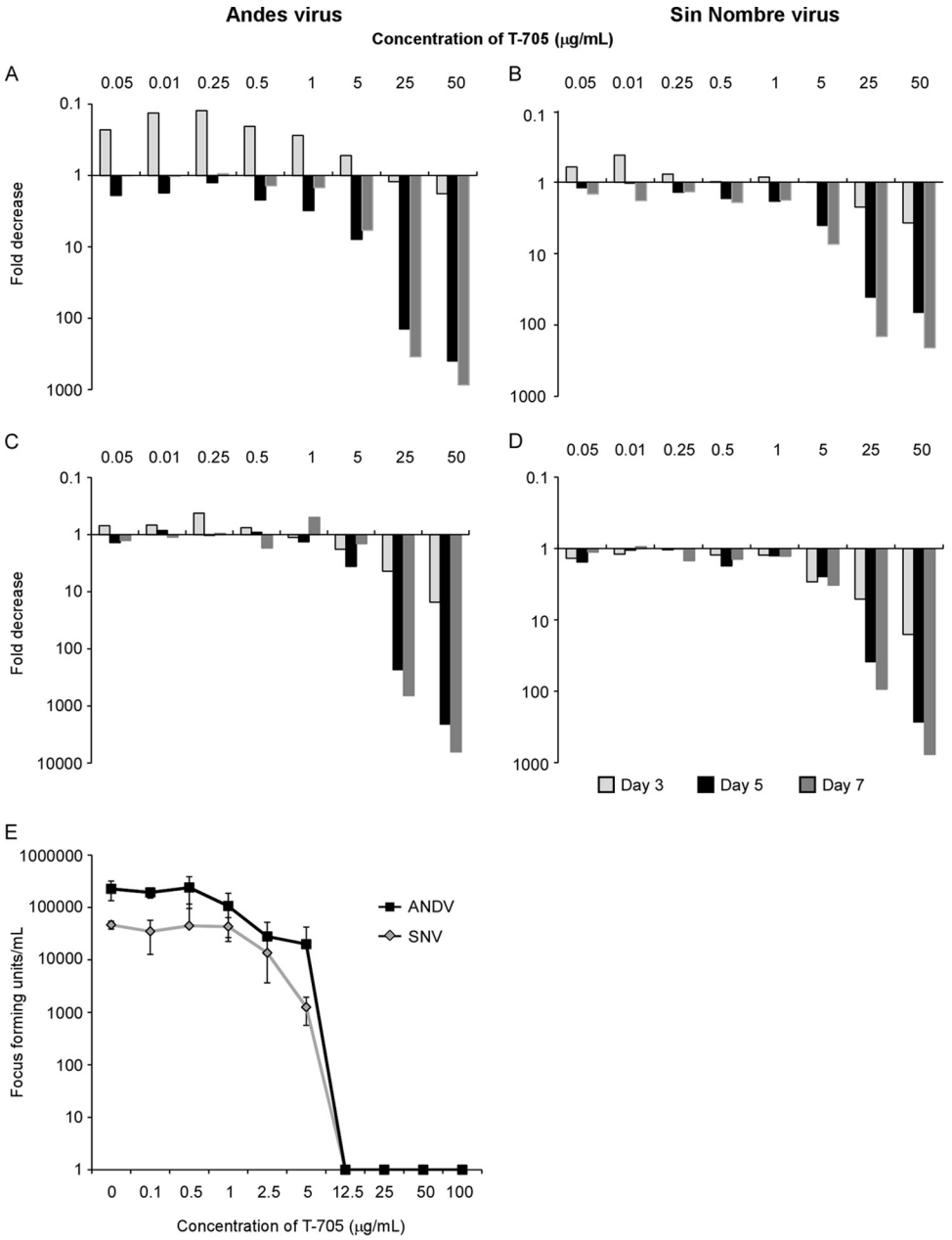

FIG 1 *In vitro* efficacy of T-705 against Andes and Sin Nombre viruses. Vero E6 cells were infected with Andes virus or Sin Nombre virus (MOI, 0.01) and were cultured in the presence of varying concentrations of T-705. Samples (cell pellets and supernatants) were collected on days 3, 5, and 7 postinfection to determine the extent of viral replication. (A through D) For both viruses, treatment with T-705 at concentrations of 25 μg/ml or greater resulted in 100- to 1,000-fold reductions in viral RNA levels in supernatants (A and B) and cell pellets (C and D) from those for matched samples collected from infected, mock-treated cells. (E) In agreement with these data, T-705 greatly reduced the levels of progeny virus, with estimated EC_{90}s between 2.5 and 5 μg/ml for both viruses. Shown are the infectious titers determined in clarified supernatant samples collected 7 days postinfection. Each point represents the average value obtained from triplicate samples. Error bars represent the standard errors of the means. The limit of detection for the focus assay was 25 infectious particles per ml.

dramatically decreased titers to effectively background levels. The maximum concentration of T-705 utilized in these studies (50 μg/ml) is well below the previously determined 50% cytotoxic concentration in Vero cells (>500 μg/ml) (18), and the absence of toxicity was confirmed by visual observation.

***In vivo* efficacy of T-705 against lethal ANDV infection.** Treatment of ANDV-infected hamsters with 50 or 100 mg of T-705/kg/day significantly reduced the severity of disease; 66.7 and 100% of treated hamsters survived infection with no apparent signs of infection (*P*, 0.0303 and 0.0011, respectively) (Fig. 2A) and no observable toxic effects of treatments. In contrast, hamsters treated daily with T-705 at 20 mg/kg or less developed lethal HPS-like disease which, as with the placebo treatment group, was essentially uniformly lethal. The lone exception was a hamster treated at 5 mg/kg/day that demonstrated signs of disease consistent with HPS but did not reach a score requiring euthanasia.

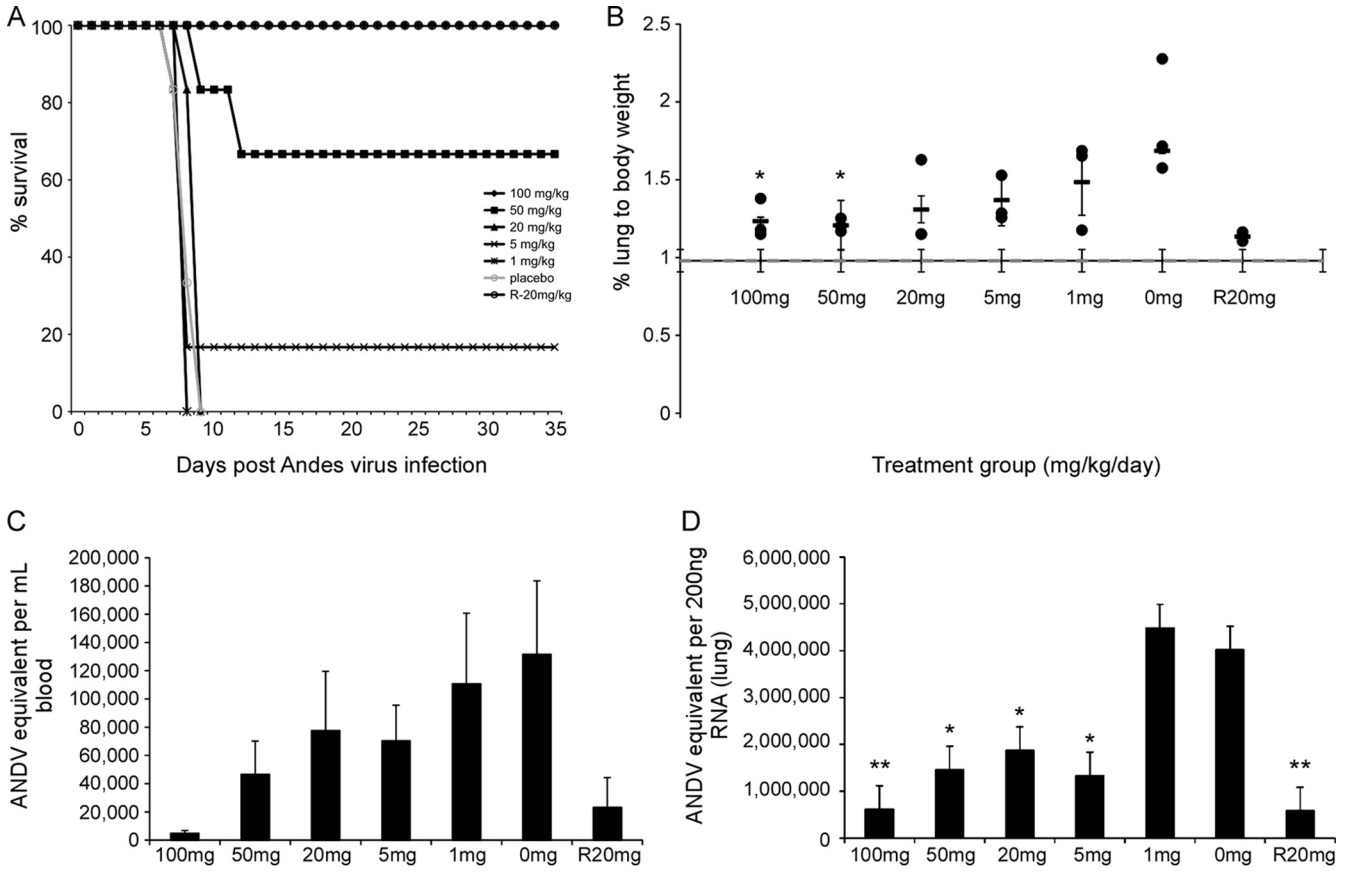

FIG 2 *In vivo* efficacy of T-705 against Andes virus. Seven groups of 9 hamsters were infected with a lethal dose of Andes virus and were treated daily with either T-705 (1, 5, 20, 50, or 100 mg/kg), 20 mg/kg ribavirin (designated R20mg), or a placebo (0 mg/kg; vehicle only) beginning 1 day postinfection. For each group, 6 hamsters were monitored for disease progression and survival, while 3 hamsters per group were euthanized for sample collection on day 8 postinfection. (A) Treatment with 50 or 100 mg of T-705/kg/day resulted in significant increases in the survival rate over that for placebo-treated control animals. (B) In agreement with the survival curves, higher lung weight-to-body weight ratios were noted for placebo-treated hamsters than for mock-infected hamsters (gray dashed line) or for groups treated daily with T-705 at 50 to 100 mg/kg. (C and D) Quantitative real-time RT-PCR was utilized to measure viral loads in tissue samples. Standards were derived from samples with known infectious titers. Dose-dependent reductions in the detection of viral RNA in blood (C) and lung (D) samples were observed, most notably for hamsters receiving T-705 at 100 mg/kg/day. Error bars represent the standard errors of the means. *, $P < 0.05$; **, $P < 0.01$.

To further determine the efficacy of daily T-705 therapy in ANDV-infected hamsters, three animals per treatment group were necropsied on day 8 postinfection. Analysis of lung weight-to-body weight ratios revealed statistically significantly higher ratios for ANDV-infected, placebo-treated hamsters than for mock-infected animals receiving treatment (100 mg of T-705/kg/day) on the same schedule ($P = 0.01$) or ANDV-infected hamsters treated with 100 or 50 mg of T-705/kg/day ($P = 0.05$) (Fig. 2B). Examination of ANDV RNA titers in blood samples revealed dose-dependent reductions in viral RNA titers in treated hamsters (Fig. 2C). Perhaps most importantly, significantly reduced levels of ANDV RNA were noted in lung samples from hamsters treated with 5, 20, or 50 mg/kg/day ($P < 0.05$) or 100 mg/kg/day ($P < 0.01$) (Fig. 2D). The qRT-PCR analysis is supported by IHC staining, which demonstrated decreased detection of viral nucleocapsid protein in lung samples from infected hamsters treated with T-705, especially those from the groups treated with higher concentrations (Fig. 3). Lung samples from control (placebo-treated) hamsters demonstrated diffuse viral antigen, primarily within pulmonary endothelial cells and a few alveolar macrophages. Similar patterns of staining were noted in hamsters treated with low (1, 5, or 20 mg/kg/day) doses of T-705. Treatment with 50 mg T-705/kg/day resulted in reduced distribution and intensity of viral staining, similar to that noted for animals that received 20 mg of ribavirin/kg/day. Hamsters receiving 100 mg T-705/kg/day had greatly reduced detection of viral antigen, with few positive cells observed.

T-705 therapy remained 100% effective at preventing lethal HPS disease in hamsters when therapy was initiated on or before day 4 postexposure (Fig. 4). Animals in these treatment groups had no overt signs of disease. In contrast, initiation of therapy on day 5 or 6 postinfection was completely ineffective at preventing or delaying HPS in hamsters. Like the placebo group, these animals demonstrated breathing abnormalities beginning on day 6 or 7 postinfection and progressing to severe respiratory distress, which was ultimately fatal by day 9. Analysis of blood samples collected from groups of hamsters immediately prior to the initiation of therapy on day 3, 4, 5, or 6 postinfection demonstrated that the dramatic loss of efficacy of T-705 coincided with the onset of viremia, as suggested by the detection of ANDV RNA in whole blood (Fig. 4, inset).

Hantavirus nucleocapsid protein-specific IgG antibodies were

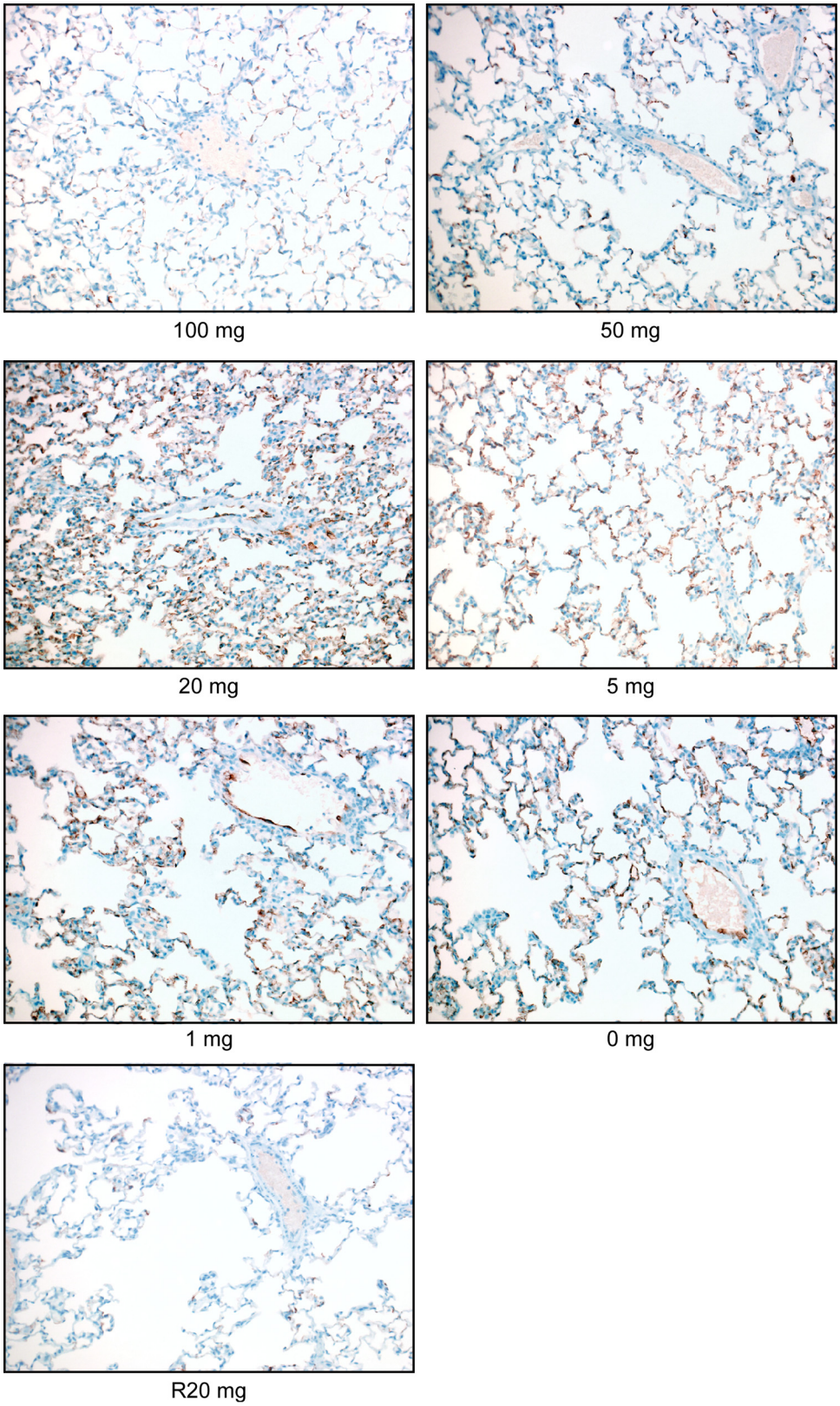

FIG 3 Immunohistochemical analysis of lungs from Andes virus-infected hamsters treated daily with T-705, ribavirin, or a placebo. Lung specimens collected at 8 days postinfection from hamsters infected with a lethal dose of Andes virus and treated daily beginning 1 day postinfection with varying concentrations of T-705, 20 mg ribavirin/kg (R20 mg), or a placebo (0 mg/kg) were tested for the presence of Andes viral antigen (nucleocapsid protein) by standard immunohistochemistry techniques. In agreement with the RT-PCR analysis, treatment with 50 or, most notably, 100 mg T-705/kg/day resulted in reduced detection of Andes viral antigen.

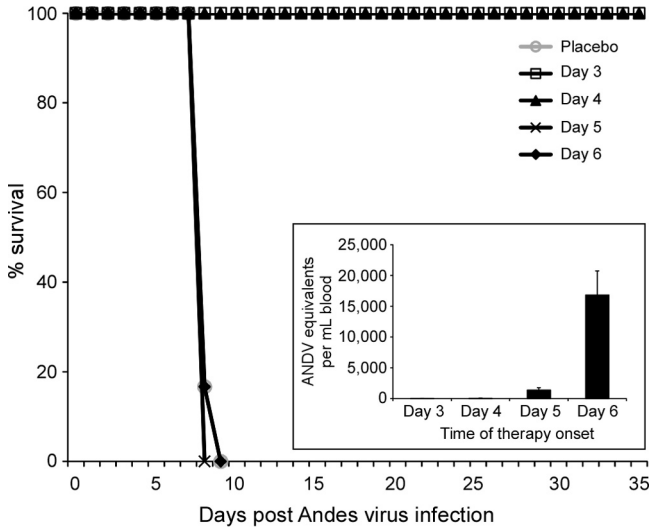

FIG 4 Efficacy of delayed T-705 therapy. Five groups of 6 hamsters were infected with a lethal dose of Andes virus. On each of days 3, 4, 5, and 6 postinfection, T-705 therapy (a 300-mg/kg loading dose, followed by daily treatment with 200 mg/kg) was initiated for a single group of animals. The fifth group received daily placebo (vehicle-only) treatments beginning 3 days postinfection. T-705 therapy remained 100% effective at preventing lethal HPS disease in hamsters when therapy was initiated on or before day 4 postinfection. (Inset) The dramatic loss of efficacy observed when therapy was initiated after day 4 coincided with the onset of viremia, as suggested by the detection of Andes virus RNA in blood samples collected from individual groups immediately prior to the commencement of treatment. Error bars represent the standard errors of the means.

detected in convalescent-phase serum samples collected from all surviving hamsters across the treatment groups. The majority (16 of 18) of hamsters treated with 100 mg of T-705/kg/day had titers of 1,600, even when therapy was initiated on day 3 or 4 postinfection, while surviving hamsters receiving T-705 at 50 or 5 mg/kg (*n*, 4 or 1, respectively) or receiving ribavirin (20 mg/kg/day) all had titers of ≥6,400.

***In vivo* efficacy of T-705 against SNV replication.** To assess the *in vivo* antiviral effect of T-705 against SNV, we utilized a recently described infection model based on a serially passaged SNV that achieves prolonged and systemic infection in Syrian hamsters (24). As in the ANDV studies, twice-daily administration of T-705 (100 mg/kg/day) reduced the detection of viral RNA in blood and, most notably, lung samples ($P < 0.0001$) collected at day 8 postinfection (Fig. 5A and B). In agreement with these findings, reductions in the detection of viral antigen were noted in lung specimens from treated hamsters. Control (placebo-treated) hamsters infected with HA-SNV demonstrated diffuse viral antigen in pulmonary endothelial cells and a few alveolar macrophages. In contrast, hamsters treated with T-705 demonstrated a significant decrease in the distribution and intensity of IHC staining, with only rare endothelial cells or macrophages that were positive for viral antigen (Fig. 5C). Interestingly, ribavirin therapy did not significantly reduce SNV RNA levels in blood and lung samples or the detection of SNV nucleocapsid antigen in lungs (Fig. 5). Combined, these data suggest that *in vivo*, SNV may be less sensitive than ANDV to the antiviral effects of ribavirin, al-

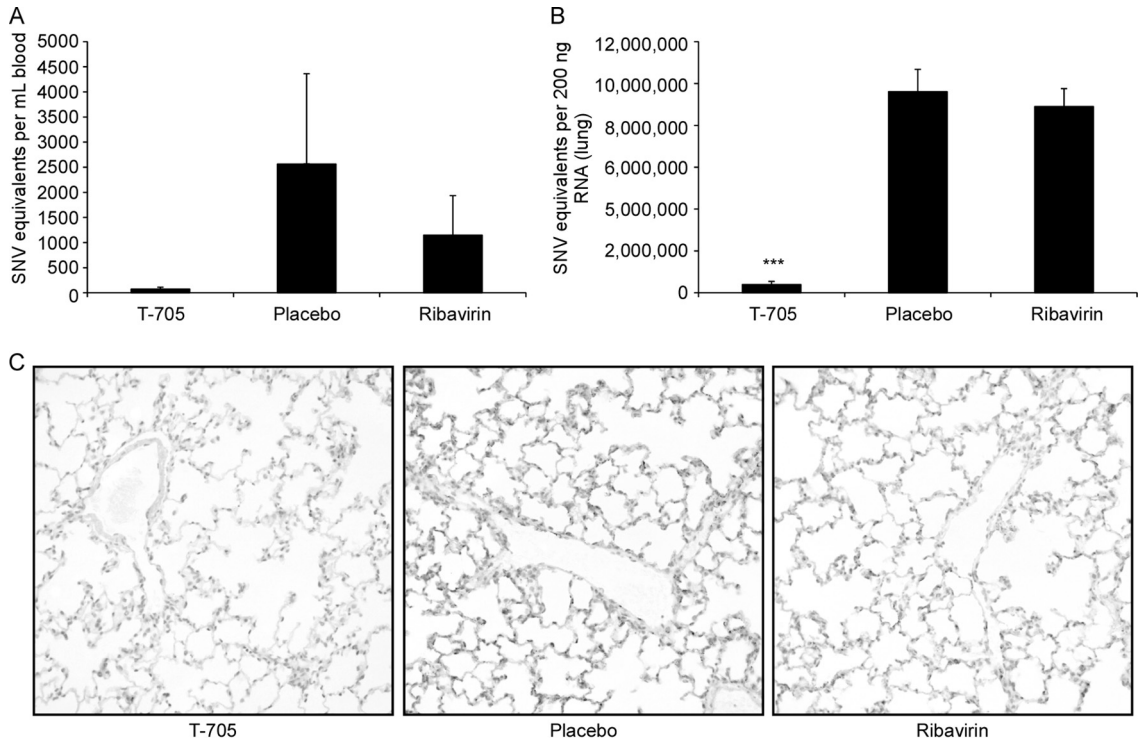

FIG 5 *In vivo* efficacy of T-705 against Sin Nombre virus. Three groups of 6 hamsters were infected with a hamster-adapted Sin Nombre virus and were treated daily, beginning 1 day postinfection, with T-705 (100 mg/kg/day), ribavirin (20 mg/kg/day), or a placebo. (A and B) Examination of blood (A) and lung (B) samples collected at 8 days postinfection revealed reductions in virus RNA levels as determined by quantitative real-time RT-PCR using standards derived from samples with known infectious titers. Error bars represent the standard errors of the means. ***, $P < 0.0001$. (C) In agreement with these findings, Sin Nombre viral nucleocapsid antigen was virtually undetectable in lung specimens from T-705-treated hamsters, in contrast to matched samples from placebo- or ribavirin-treated animals.

though further experiments with a wider dosage range would be required to clarify these findings.

DISCUSSION

Vaccination is the primary public health countermeasure for viral pathogens worldwide, and based on the high incidence of disease associated with Old World hantaviruses, especially across Asia, a vaccine for HFRS would be advantageous (28). However, the sporadic nature and relatively low frequency of HPS cases suggest that alternative measures, specifically antivirals and therapeutics, should be considered for treating infections with New World hantaviruses. Currently the treatment of HPS is predominantly supportive care, although extracorporeal membrane oxygenation (ECMO) is utilized for severe cases in some medical centers (12). The periodic nature of HPS cases makes evaluation of the efficacy of specific therapies difficult in a clinical setting, and despite the development of a hamster model of HPS, few therapeutics or antivirals have been evaluated *in vivo*. To date, the only compound that has been assessed in a clinical setting is ribavirin, which was found to be largely ineffective against the advanced stages of HPS (10, 11).

The complexity of HPS and the difficulties in treating disease are illustrated not only by the high mortality rates in humans but also by the paucity of studies published to date that have effectively protected hamsters from lethal HPS-like disease postexposure. Administration of neutralizing antibodies on or before day 5 post-intramuscular challenge or day 8 post-intranasal challenge can prevent the development of lethal HPS associated with ANDV infection in hamsters (29–31). Initiation of daily ribavirin therapy on or before day 3 post-intraperitoneal challenge also prevents lethal HPS in hamsters (9). When one considers the differences in disease progression associated with the various challenge routes utilized in these studies, the treatment options tested thus far appear unable to prevent lethal HPS in hamsters after the onset of viremia. In the current study, T-705 remained effective at preventing HPS in hamsters when therapy was initiated on or before day 4 postinfection. The dramatic loss of efficacy observed when T-705 therapy was initiated on day 5 postinfection correlated with the first detection of ANDV RNA in whole-blood samples collected from hamsters immediately prior to therapy onset (Fig. 4). There is increasing evidence that both HFRS and HPS are associated with excessive and deleterious host immune responses in humans, which lead to the severe disease manifestations observed (2). In hamsters infected by intranasal instillation of ANDV, the onset of viremia coincides with increased proinflammatory and Th1 and Th2 immune responses in the lungs and hearts of infected animals (32). Based on these findings as well as the current understanding of hantavirus pathogenesis and the rapid progression of HPS in humans, treatment strategies after the onset of symptoms will likely require a multifaceted approach aimed at reducing virus replication, reversing the aberrant host immune responses, and improving vascular barrier function. However, the host signaling pathways responsible for the aberrant immune responses associated with the development of HPS remain uncertain. As a result, few immunomodulatory compounds have been tested *in vivo*, and none have demonstrated a significant positive effect (12, 33).

Although ribavirin is licensed for use in the treatment of viral infections, including respiratory syncytial virus infections, and as a part of combination therapy for hepatitis C virus, in addition to off-label therapy for Lassa fever, Crimean-Congo hemorrhagic fever, and HFRS, treatment is associated with adverse side effects, including anemia. In these studies, we have demonstrated the inhibitory effects of a second potent antiviral agent, T-705, which is effective at preventing lethal disease in the hamster model of HPS. Importantly, by use of body surface area conversions (34), T-705 concentrations of 100 to 200 mg/kg/day in hamsters translate to equivalent doses of 14 to 28 mg/kg/day in humans, which are consistent with the T-705 doses evaluated in the recent phase II clinical dose-finding study for the treatment of uncomplicated influenza (35). As with ribavirin, the efficacy of T-705 depends on the time of administration; however, based on the excellent safety record of this agent in animals and humans, T-705 represents an improved candidate compound for utilization in monotherapy against suspected exposures (i.e., laboratory incidents, close contacts with HPS cases, or rodent bites), as well as for combination therapeutic approaches in a clinical setting.

ACKNOWLEDGMENTS

This work was supported in part by the Division of Intramural Research (DIR) of the National Institutes of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH). B.B.G. was supported by NIH grant U54 AI-065357 (Rocky Mountain Regional Center of Excellence for Biodefense and Emerging Infectious Disease Research).

We thank the Rocky Mountain Veterinary Branch for assistance in animal procedures, Elaine Haddock and Friederike Feldmann for technical assistance, Tina Thomas, Rebecca Rosenke, and Dan Long for preparing tissue samples for histological analysis, and Anita Mora for help in preparing the figures (all from DIR, NIAID, NIH).

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